IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Patent of | : | Wilhelm, et al. |
| Patent No. | : | 6,680,320 |
| For | : | UROKINASE INHIBITORS |
| Control No. | : | 90/007,935 |
| Filed | : | July 26, 2002 |
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| TC/A.U. | : | 3991 |
| Examiner | : | Bennett Celsa |
| Docket No. | : | 2923-236 |
| Customer No. | : | 6449 |
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**DECLARATION**

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Roger B. Cohen, declare as follows.

1. I am a scientist and a medical oncologist, and I am conducting a Phase I clinical trial of WX-UK1 for Wilex AG, the current Patent Owner of the above-captioned U.S. patent. I am also a member of the Medical Advisory Board of Wilex AG.

2. I am currently Director of Phase I Program at the Fox Chase Cancer Center in Philadelphia. Prior to my current position, my experience includes a position as Associate Professor of Medicine (with tenure) in the Division of Hematology-Oncology at the University of Virginia where I was Director of the Cancer Center Clinical Trials Office. Before that I served as Deputy Director of the Division of Monoclonal Antibodies at the USA Food and Drug Administration Center for Biologics Evaluation and Research. I received my M.D. degree from Harvard Medical School, and did my

medical residency in internal medicine and hematology at the Mount Sinai Hospital in New York City and my oncology fellowship at the National Cancer Institute.

3. I am of the opinion based on my own experience, observations, and review of the data that WX-UK1 is pharmaceutically acceptable and represents a promising cancer treatment. WX-UK1 has been tested in cancer patients in two clinical Phase Ib studies. The two studies, conducted at several centers in Germany, evaluated the safety, pharmacokinetics and biological activity of rising doses of WX-UK1 as a monotherapy in patients with advanced solid tumors, and in patients with head & neck cancer. The compound was safe and well tolerated at all doses tested. It was quite noteworthy that despite broad-spectrum inhibition *in vitro* of several key serine proteases related to blood clotting, making bleeding and clotting significant safety concerns at the time the trials were designed, there were no observations of bleeding or thrombosis in these studies. In our USA study we gave WX-UK1 in combination with capecitabine to patients with advanced solid tumors lacking better treatment options. In this study, WX-UK1 was also well-tolerated, without significant clinical or laboratory toxicity, and most importantly, did not exacerbate the toxicities of capecitabine chemotherapy or cause an excess of bleeding or thrombosis. Detailed pharmacokinetics studies did not indicate any clinically important drug-drug interactions between capecitabine and WX-UK1. We noted that several of our patients had prolonged stable disease while receiving the combination of WX-UK1 plus capecitabine, an observation that suggests anti-tumor efficacy.

4. The results described above, including the pharmaceutical acceptability and absence of significant clinical or laboratory toxicities, are somewhat unexpected, especially in view of the broad spectrum of protease inhibitory activities of WX-UK1. In the late nineties (circa 1998) it was a widely held scientific hypothesis and working principle of drug development in the area of metastasis that uPA inhibitors suitable for cancer therapy would need to have a high degree of specificity for inhibition of uPA (against tPA and plasmin). It is therefore quite noteworthy that WX-UK1 does not fulfill this criterion at all, possessing instead a very broad-spectrum anti-protease activity. On this basis at that time WX-UK1 would have been considered by most experts to be a poor candidate for clinical development because of concerns about promiscuous anti-protease activity resulting in multiple off-target effects thereby causing unacceptable toxicity especially in the clotting system. I am of the opinion that the data shown in the tables of the 1997 and 1998 Pentapharm Catalogues indicate that WX-UK1 does not have the desired degree of target selectivity that was felt to be an important feature of a clinically useful uPA inhibitor. Instead, the tables indicate that WX-UK1 has very low Ki values for plasmin and uPA. Furthermore, the Ki values of WX-UK1 for uPA in the tables are very similar to those shown for the other tested enzymes. Based on the tables in the Pentapharm catalogues I would have concluded that WX-UK1 would be ineffective, if not unacceptable for development as an anti-invasive or anti-proliferative cancer therapeutic and would therefore not warrant clinical testing in view of the data shown in the tables.

5. As noted WX-UK1 is a broad-spectrum protease inhibitor with relatively poor selectivity for uPA. Indeed, WX-UK1 has such poor selectivity for uPA against blood clotting cascade enzymes including tPA and plasmin that I would have classified WX-UK1 differently from amiloride and B428, which, by contrast, were considered attractive uPA inhibitors for clinical development based on their high selectivity for uPA. Unlike amiloride or B428, which were classified as selective uPA inhibitors, I would have classified WX-UK1 as a general serine protease inhibitor with strong inhibitory activities for a broad spectrum of blood clotting cascade enzymes. Thus, I do not believe that any person having ordinary skill in the art would have considered WX-UK1 analogous to amiloride or B428 for the purpose of predicting its potential application to pharmaceutical use as an anti-invasive or anti-proliferative agent for the treatment of cancer.

6. I state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Roger B. Cohen, M.D.

Dec 21, 2006
Date